(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 October 2003 (16.10.2003)

PCT

(10) International Publication Number
WO 03/084526 A1

(51) International Patent Classification[7]: A61K 31/205, 31/22, A61P 15/08, A23L 1/29

(21) International Application Number: PCT/IT03/00214

(22) International Filing Date: 8 April 2003 (08.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
RM2002A000194 9 April 2002 (09.04.2002) IT

(71) Applicant *(for all designated States except US)*: **SIGMA-TAU HEAL THSCIENCE S.P.A.** [IT/IT]; Via Treviso 4, I-00040 Pomezia RM (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CAVALLINI, Giorgio** [IT/IT]; c/o Sigma-Tau Healthscience S.p.A., Via Treviso 4, I-00040 Pomezia RM (IT). **BIAGIOTTI, Giulio** [IT/IT]; c/o Sigma-TAu Healthscience S.p.A., Via Treviso 4, I-00040 Pomezia RM (IT). **KOVERECH, Aleardo** [IT/IT]; c/o Sigma-TAu Healthscience S.p.A., Via Treviso 4, I-00040 Pomezia RM (IT). **SARDELLI, Francesca** [IT/IT]; c/o Sigma-TAu Healthscience S.p.A., Via Treviso 4, I-00040 Pomezia RM (IT).

(74) Agent: **CAVATTONI, Fabio**; Cavattoni - Raimondi, Viale dei Parioli, 160, I-00197 Roma (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/084526 A1

(54) Title: COMBINED USE OF L-CARNITINE, ACETYL L-CARNITINE AND PROPIONYL L-CARNITINE FOR THE TREATMENT OF OLIGOASTHENOTERATOSPERMIA

(57) Abstract: The use is described of L-carnitine, acety L-carnitine and propionyl L-carnitine, or of one of their pharmaceutically acceptable salts for the preparation of a medicine for the treatment of oligoasthenoteratospermia of any origin.

COMBINED USE OF L-CARNITINE, ACETYL L-CARNITINE AND PROPIONYL L-CARNITINE FOR THE TREATMENT OF OLIGOASTHENOTERATOSPERMIA

The invention described herein relates to the use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine, in combination, for the preparation of a medicine for the treatment of oligoasthenoteratospermia of any origin: inflammatory, idiopathic, hormonal, or associated with varicocele.

The final common pathway of all these forms of infertility is the local accumulation of oxygen free radicals (Pasqualotto F.F. et al., Fertil. Steril. 73:459-464, 1999). To combat this accumulation antioxidant drugs can be used.

Most of the antioxidants currently available on the pharmaceutical market (vitamin E, glutathione, NADH) act in a manner unrelated to the Krebs cycle, and therefore in a manner related solely to the drug dosage and not to cell metabolism.

The substantial topographical and temporal heterogeneousness (within the same testicle) of human spermatogenesis (Silber S. J., Clin. Obstet. Gynaecol. 43:843-888, 1999) makes it impossible to establish a "fixed" dosage of antioxidants, since this would lead to over- and underdosing.

An excessive lowering of oxygen free radicals leads to inhibition of the acrosome and capacitation reaction of the spermatozoa (Ochendorf F.R., Hum. Reprod. Update. 5:399-402,1999), whereas too high a concentration leads to morphological abnormalities of the spermatozoon itself (Gattuccio F., et. al., Varicocele 2000, Cofese Editore, Palermo 2000).

In Human Reprod. 13:3090-3093, 1998, a semiquantitative scoring sysem has been proposed based on US Doppler results to distinguish between obstructive and non-obstructive azoospermias.

In Human. Reprod. 15:2554-2558, 2000, it is reported that the transmediastinic testicular artery has a significantly greater resistivity index in non-obstructive azoospermic subjects than in controls and in oligoasthenospermic subjects.

In Fertil. Steril. 75:1088-1094, 2001, it is reported that the pulsatility index of the testicular artery is higher in obstructive than in non-obstructive azoospermia.

In J. Urol. 163:135, 2000, it is reported that intratesticular blood flow and blood flow rate are significantly lower in subjects with arrested maturation of spermatogenesis, that is to say with hypoplasia of the germ cells.

The spermatozoa are produced in the testicles and undergo post-gonadal maturation in the epididymis in order to acquire their fertilising capacity.

In plasma, high-molecular-weight proteins and small molecules such as the free carnitines facilitate the maturation of the gametes into competent, functional cells.

Epididymal L-carnitine, which comes from the plasma, has a beneficial effect on the spermatozoa. It passes into the spermatozoa by passive diffusion and is acetylated only in mature spermatozoa.

The relationship between the endogenous pool of free and acetylated carnitines and the progressive percentage of sperm motility indicate a more important metabolic function related to flagellar movement.

Thus, the start of sperm motility, in the epididymis, is probably independent of the carnitine system, while the energy properties of acetyl L-carnitine are relevant in "energy crisis" situations.

The accumulation of free carnitines in the cytoplasm in mature spermatozoa has to be regarded as a protective form of the mitochondrial metabolism which is useful for the survival of these isolated cells.

The use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine in combination is already known.

In European patent EP 0 973 415, a dietetic composition is described consisting of L-carnitine, acetyl L-carnitine and propionyl L-carnitine, which is useful for athletes subject to intense physical effort, or for asthenic individuals.

In patent application WO 99/17623, a dietetic composition is described consisting of L-carnitine, acetyl L-carnitine and propionyl L-carnitine for the treatment of alcohol withdrawal syndrome.

Also known is the use of L-carnitine and of the alkanoyl L-carnitines for the treatment of male infertility.

In Drugs Exptl. Clin. Res. XXI(4):157-159, 1995, it is reported that the administration of L-carnitine, in a group of patients with idiopathic asthenospermia, improves sperm motility and increases the sperm count in 37 out of 47 patients treated.

In Dermatol. Monatschr. 169:572-575, 1983, the same results are confirmed.

In Andrologia, 26:155-159, 1994, it is reported that the administration of L-carnitine in infertile patients brings about a significant improvement of both a quantitative and qualitative nature in sperm motility.

In Fertilität 4:1-4, 1988, it is reported that L-carnitine therapy in infertile patients brings about an increase in carnitine levels in the

spermatozoa and at the same time an increase in sperm motility and sperm count.

Loumbakis P., et al. (12th Congress of the European Asso-ciation of Urology, Paris, 1-4 September, 1996) report preliminary data indicating that the administration of L-carnitine may have a positive effect on sperm quality.

In Acta Eur. Fertil. 23(5):221-224, 1992, it is reported that the use of acetyl L-carnitine in patients with idiopathic oligoastheno-spermia has no effect upon sperm density, but induces a progressive increase in sperm motility.

In US 6,090,848, it is reported that the combination of L-carnitine and acetyl L-carnitine is useful for the treatment of oligoasthenoteratospermia.

The above-mentioned known compounds are certainly to be regarded as good therapeutic agents, but nevertheless present a number of disadvantages.

In fact, as mentioned above, in Drugs Exptl. Clin. Res. XXI (4):157-159, 1995, it is reported that the administration of L-carnitine to a group of patients with idiopathic oligoasthenoteratospermia improves the sperm count and increases sperm motility in 37 out of 47 patients treated, whereas, in Acta Eur. Fertil. 23(5):221-224, 1992, it is reported that the use of acetyl L-carnitine in patients with idiopathic oligoasthenospermia has no effect upon sperm density.

The combination described in US 6,090,848, which is to be regarded as the best one known to date, was used as a reference compound during the study of the activity of the composition according to the present invention. The results obtained, reported here below, confirmed the activity of the composition described in US 6,090,848, but also demonstrated, surprisingly and unexpectedly, that the combination

according to the present invention is more active than the composition described in US 6,090,848.

In the medical field, there is still a strongly perceived need for the availability of compositions useful for the treatment of oligoasthenoteratospermia, which do not present the disadvantages of the above-mentioned known compounds, or which improve the results obtained with the best of the known compositions currently in use.

It has now been found that the use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine or of one of their pharmaceutically acceptable salts, in combination, has proved capable of exerting a surprising synergistic effect in the treatment of all forms of oligo-asthenoteratospermia.

One object of the present invention therefore is the use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine inner salts or their pharmaceutically acceptable salts for the preparation of a medicine for the treatment of oligoasthenoteratospermia.

A further object of the present invention is the use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine inner salts or their pharmaceutically acceptable salts, for the preparation of a medicine for the treatment of oligospermia.

A further object of the present invention is the use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine inner salts or their pharmaceutically acceptable salts, for the preparation of a medicine for the treatment of asthenospermia.

A further object of the present invention is the use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine inner salts or their pharmaceutically acceptable salts, for the preparation of a medicine for the treatment of teratospermia.

A further object of the present invention is the use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine or their pharmaceutically acceptable salts, for the preparation of a nutritional composition for the treatment of oligoasthenoteratospermia.

A further object of the present invention is the use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine or their pharmaceutically acceptable salts, for the preparation of a nutritional composition for the treatment of oligospermia.

A further object of the present invention is the use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine or their pharmaceutically acceptable salts, for the preparation of a nutritional composition for the treatment of asthenospermia.

A further object of the present invention is the use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine or their pharmaceutically acceptable salts, for the preparation of a nutritional composition for the treatment of teratospermia.

It has been found that the combination according to the present invention is more active than the combination of L-carnitine and acetyl L-carnitine mentioned above, in improving both sperm count and sperm motility in man.

The L-carnitine, acetyl L-carnitine and propionyl L-carnitine can be in any form suitable for oral or parenteral administration in man.

L-carnitine, acetyl L-carnitine and propionyl L-carnitine can be formulated together, as a mixture, or can be formulated separately (packaged separately), using known methods. L-carnitine, acetyl L-carnitine and propionyl L-carnitine can be administered to an individual either when fomulated in a mixture or when formulated in separate packs.

On the basis of various factors, such as the concentration of the active ingredients or the patient's condition, the combination according to the present invention can be marketed as a health food supplement, a nutritional supplement, or as a therapeutic product on sale with or without the need for a medical prescription.

According to the present invention, the molar ratio of L-carnitine to acetyl L-carnitine and propionyl L-carnitine or of one of their pharmaceutically acceptable salts ranges from 2.48:0.098:0.092 to 0.186:0.98:0.92.

Alternative molar ratios include the molar ratios ranging from 2.48:0.49:0.46 to 0.62:0.49:0.46.

Alternative molar ratios include the molar ratios ranging from 2.48:0.98:0.92 to 1.24:0.49:0.23.

The combination preparation according to the present invention, when in unit dosage form, contains from 4.0 g to 0.30 g of L-carnitine inner salt, from 0.20 to 2.0 g of acetyl L-carnitine inner salt and from 0.20 g to 2.0 g of propionyl L-carnitine inner salt, or an equimolar amount of one of their pharmaceutically acceptable salts.

The preferred combination preparation, in unit dosage form, contains 2 g of L-carnitine inner salt, 1 g of acetyl L-carnitine inner salt and 0.5 g of propionyl L-carnitine inner salt, or an equimolar amount of one of their pharmaceutically acceptable salts.

It has been found, however, that, although the daily dose of the above-mentioned active ingredients to be administered depends on the patient's age, weight and condition, using professional experience it is generally advisable to administer, in a single dose or in multiple doses, from 0.3 to 4.0 g/day approx. of L-carnitine, from 0.20 to 2.0 g/day approx. of acetyl L-carnitine, and from 0.20 to 2.0 g/day approx. of propionyl L-carnitina, or an equimolar amount of one of their

pharmaceutically acceptable salts.

Larger doses can be administered thanks to the extremely low toxicity of said active ingredients.

Reported here below is a clinical trial conducted in order to assess whether or not the combination according to the present invention improves sperm motility as compared to combined therapy with L-carnitine plus acetyl L-carnitine.

The patients recruited had to fulfil the following inclusion/exclusion criteria.

Inclusion criteria: young infertile males with astheno-zoospermia recognised as being the sole cause of infertility over the preceding period of at least two years; the semen criteria that had to be fulfilled in at least two samples were: sperm concentration (M/ml) from 10 to 20, motility (%) >20 <40 at 2 hours, rapid linear progression (%) <20 at 2 hours. The patients were subjected to history taking, bilateral scrotal echo-colour Doppler, physical examination, hormone assays (free and total testosterone, FSH, LH, 17 beta oestradiol, progesterone, prolactin), and a spermiogram (WHO 1999).

Exclusion criteria: acute genital inflammation, sperm concentration <5,000,000/ ml. All patients gave their informed consent for participation in this open trial. In all, the patients examined were 8 patients with varicocele (6 grade II, 2 grade III), 12 parients with chronic inflammation of the sex glands, 12 patients with varicocele (8 grade II, 4 grade III) + chronic inflammation of the sex glands, 25 with cryptogenetic oligoasthenospermia, 2 with hypogonadotropic hypogonadism, 1 with hyperprolactinaemia, 4 with a history of surgery (unilateral cryptorchidia in 3 cases, bilateral in 1 case) and 2 with bilateral testicular trauma.

Semen was obtained by masturbation after at least 4 days of sexual abstinence. Semen samples were analysed within one hour of ejaculation for all parameters, using the standard methods recommended by the WHO (1987). Sperm motility was studied using a computerised motility analyser on at least two samples.

Semen analysis and the motility assessment were carried out before treatment with the study compounds and after 4 months' treatment with the latter.

L-carnitine was administered at the dose of 2 g/day (2 x 500 mg tablets twice daily, after lunch) for 4 months; acetyl L-carnitine was administered at the dose of 1 g/day for 4 months, while propionyl L-carnitine was administered at the dose of 500 mg/ day for 4 months.

The combination according to the present invention significantly increases the sperm concentration and motility as well as the percentage of spermatozoa with a rapid linear progression as compared to treatment with the L-carnitine plus acetyl L-carnitine combination, regardless of the cause of the oligoasthenoterato-spermia, even in patients with hormonal abnormalities.

In the latter, the combination according to the invention has permitted a reduction in the posology of gonadotropins and antiprolactinaemia drugs compared to the data reported in the literature.

The medicine according to the invention described herein can be prepared by mixing the active ingredients (L-carnitine inner salt, acetyl L-carnitine inner salt and propionyl L-carnitine inner salt or one of their pharmacologically acceptable salts) with suitable excipients for the fomulation of compositions for enteral (particularly oral) or parenteral (particularly intramuscular of intravenous) administration. Experts in pharmaceutical technology are familiar with said excipients.

The pharmaceutically acceptable salts of the above-mentioned active ingredients include all the pharmaceutically acceptable salts that are prepared by addition of an acid to the L-carnitine, acetyl L-carnitine and propionyl L-carnitine inner salt, and that do not give rise to unwanted toxic or side effects. The formation of salts by addition of an acid is well known in pharmaceutical technology.

Examples of such salts, though not exclusively these, are: chloride, bromide, orotate, aspartate, acid aspartate, citrate, acid citrate, magnesium citrate, phosphate, acid phosphate, fumarate, acid fumarate, magnesium fumarate, glycerophosphate, lactate, maleate and acid maleate, mucate, oxalate, acid oxalate, pamoate, acid pamoate, sulphate, acid sulphate, glucose phosphate, tartrate, acid tartrate, magnesium tartrate, 2-amino ethane sulphonate, magnesium 2-amino ethane sulphonate, methane sulphonate, choline tartrate, trichloroacetate and trifluoroacetate.

Claims

1. Use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine inner salts, or of their pharmaceutically acceptable salts, for the preparation of a medicine for the treatment of oligoasthenoteratospermia.

2. Use according to claim 1, for the preparation of a medicine for the treatment of oligospermia.

3. Use according to claim 1, for the preparation of a medicine for the treatment of asthenospermia.

4. Use according to claim 1, for the preparation of a medicine for the treatment of teratospermia.

5. Use of L-carnitine, acetyl L-carnitine and propionyl L-carnitine or their pharmaceutically acceptable salts, for the preparation of a nutritional composition for the treatment of oligoasthenoteratospermia.

6. Use according to claim 5, for the preparation of a nutritional composition for the treatment of oligospermia.

7. Use according to claim 5, for the preparation of a nutritional composition for the treatment of asthenospermia.

8. Use according to claim 5, for the preparation of a nutritional composition for the treatment of teratospermia.

9. Use according to claim 1 or 5 in which the pharmaceutically acceptable salt is selected from the group consisting of chloride, bromide, orotate, aspartate, acid aspartate, citrate, acid citrate, magnesium citrate, phosphate, acid phosphate, fumarate, acid fumarate, magnesium fumarate, glycerophosphate, lactate, maleate

and acid maleate, mucate, oxalate, acid oxalate, pamoate, acid pamoate, sulphate, acid sulphate, glucose phosphate, tartrate, acid tartrate, magnesium tartrate, 2-amino ethane sulphonate, magnesium 2-amino ethane sulphonate, methane sulphonate, choline tartrate, trichloroacetate and trifluoroacetate.

10. Use according to any one of the preceding claims, in which the L-carnitine, acetyl L-carnitine and propionyl L-carnitine inner salts or their pharmaceutically acceptable salts are in a mixture or are packaged separately.

11. Use according to claim 10, in which the molar ratio of L-carnitine to acetyl L-carnitine and propionyl L-carnitine or of their pharmaceutically acceptable salts ranges from 2.48:0.098:0.092 to 0.186:0.98:0.92.

12. Use according to claim 10, in cui the molar ratio of L-carnitine to acetyl L-carnitine and propionyl L-carnitine or of their pharmaceutically acceptable salts ranges from 2.48:0.49:0.46 to 0.62:0.49:0.46.

13. Use according to claim 10, in which the molar ratio of L-carnitine to acetyl L-carnitine and propionyl L-carnitine or of their pharmaceutically acceptable salts ranges from 2.48:0.98:0.92 to 1.24:0.49:0.23.

14. Use according to claim 11, in which the medicine or the nutritional composition in unit dosage form contains L-carnitine inner salt in amounts ranging from 4.0 g to 0.30 g, acetyl L-carnitine inner salt in amounts ranging from 0.20 to 2.0 g, and propionyl L-carnitine inner salt in amounts ranging from 0.20 g to 2.0 g, or equimolar amounts of their pharmaceutically acceptable salts.

15. Use according to claim 14, in which the unit dosage form contains 2 g of L-carnitine inner salt, 1 g of acetyl L-carnitine inner

salt and 0.5 g of propionyl L-carnitine inner salt or equimolar amounts of their pharmaceutically acceptable salts.

INTERNATIONAL SEARCH REPORT

PCT 03/00214

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/205 A61K31/22 A61P15/08 A23L1/29

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data, PASCAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 27925 A (SIGMA TAU HEALTHSCIENCE SPA) 10 June 1999 (1999-06-10) cited in the application claims	1-15
Y	EP 0 539 336 A (SIGMA TAU IND FARMACEUTI) 28 April 1993 (1993-04-28) claims 1,4	1-15
A	WO 98 43499 A (CAVAZZA CLAUDIO ;SIGMA TAU IND FARMACEUTI (IT)) 8 October 1998 (1998-10-08) cited in the application abstract	1-15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 August 2003	22/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Pacreu Largo, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 17623 A (CAVAZZA CLAUDIO ;FASSI ALDO (IT); SIGMA TAU IND FARMACEUTI (IT)) 15 April 1999 (1999-04-15) abstract ---	1-15
A	COSTA M ET AL: "L-CARNITINE IN IDIOPATHIC ASTHENOZOOSPERMIA: A MULTICENTER STUDY" ANDROLOGIA, BLACKWELL, BERLIN, DE, vol. 26, May 1994 (1994-05), pages 155-159, XP008014043 ISSN: 0303-4569 cited in the application abstract ---	1-15
A	MONCADA M L ET AL: "EFFECT OF ACETYLCARNITINE TREATMENT IN OLIGOASTHENOSPERMIC PATIENTS" ACTA EUROPAEA FERTILITATIS, PICCIN MEDICAL BOOKS, PADOVA,, IT, vol. 23, no. 5, 1992, pages 221-224, XP008014044 ISSN: 0587-2421 cited in the application abstract -----	1-15

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9927925	A	10-06-1999	US	5863940 A	26-01-1999
			US	6090848 A	18-07-2000
			AT	206916 T	15-11-2001
			AU	749754 B2	04-07-2002
			AU	1259199 A	16-06-1999
			BR	9814711 A	03-10-2000
			CA	2314942 A1	10-06-1999
			CN	1284871 T	21-02-2001
			DE	69802113 D1	22-11-2001
			DE	69802113 T2	06-06-2002
			DK	1039894 T3	11-02-2002
			EE	200000309 A	15-08-2001
			EP	1039894 A1	04-10-2000
			ES	2163896 T3	01-02-2002
			HU	0004562 A2	28-05-2001
			WO	9927925 A1	10-06-1999
			JP	2001524520 T	04-12-2001
			NO	20002798 A	27-06-2000
			PL	342115 A1	21-05-2001
			PT	1039894 T	29-04-2002
			SI	1039894 T1	28-02-2002
			SK	7572000 A3	07-11-2000
			TR	200001519 T2	21-11-2000
			US	2002058632 A1	16-05-2002
			US	6235784 B1	22-05-2001
			US	2003008921 A1	09-01-2003
			US	2001018455 A1	30-08-2001
EP 0539336	A	28-04-1993	IT	1249462 B	23-02-1995
			EP	0539336 A1	28-04-1993
			JP	5194207 A	03-08-1993
			KR	137009 B1	25-04-1998
WO 9843499	A	08-10-1998	IT	RM970185 A1	01-10-1998
			AT	202675 T	15-07-2001
			AU	729412 B2	01-02-2001
			AU	6746298 A	22-10-1998
			BR	9807905 A	22-02-2000
			CN	1251496 T	26-04-2000
			DE	69801047 D1	09-08-2001
			DE	69801047 T2	31-10-2001
			DK	973415 T3	24-09-2001
			EP	0973415 A2	26-01-2000
			ES	2159179 T3	16-09-2001
			GR	3036777 T3	31-01-2002
			HK	1026124 A1	19-04-2002
			IL	131857 A	21-04-2002
			WO	9843499 A2	08-10-1998
			JP	2001517085 T	02-10-2001
			PT	973415 T	30-10-2001
			SK	134999 A3	16-05-2000
			US	6245378 B1	12-06-2001
WO 9917623	A	15-04-1999	IT	1295408 B1	12-05-1999
			AT	220860 T	15-08-2002
			AU	730740 B2	15-03-2001
			AU	9366098 A	27-04-1999
			BG	104286 A	30-11-2000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9917623 A		BR 9812604 A	01-08-2000
		CA 2305598 A1	15-04-1999
		CN 1092939 B	23-10-2002
		CZ 20001207 A3	15-11-2000
		DE 69806788 D1	29-08-2002
		DE 69806788 T2	03-04-2003
		DK 1022960 T3	04-11-2002
		EA 2177 B1	28-02-2002
		EE 200000235 A	15-06-2001
		EP 1022960 A1	02-08-2000
		ES 2180200 T3	01-02-2003
		HU 0004336 A2	28-05-2001
		WO 9917623 A1	15-04-1999
		JP 2001518484 T	16-10-2001
		NO 20001688 A	02-06-2000
		NZ 503663 A	30-11-2001
		PL 339621 A1	02-01-2001
		PT 1022960 T	31-12-2002
		SI 1022960 T1	31-10-2002
		SK 4762000 A3	09-10-2000
		US 6255346 B1	03-07-2001